Effect of Exercise Training on Postexercise Oxygen Uptake Kinetics in Patients With Reduced Ventricular Function*

Jonathan Myers, PhD; Renato Gianrossi, MD; Juerg Schwitter, MD; Doris Wagner, MD; and Paul Dubach, MD

Background: The time required for oxygen uptake ($\dot{V}o_2$) to return to baseline level (recovery kinetics) is prolonged in patients with reduced ventricular function, and the degree to which it is prolonged is related to the severity of heart failure, markers of abnormal ventilation, and prognosis. In the present study, we sought to determine the effect of exercise training on $\dot{V}o_2$ recovery kinetics in patients with reduced ventricular function.

Methods: Twenty-four male patients with reduced ventricular function after a myocardial infarction were randomized to either a 2-month high-intensity residential exercise training program or to a control group. $\dot{V}o_2$ kinetics in recovery from maximal exercise were calculated before and after the study period and expressed as the slope of a single exponential relation between $\dot{V}o_2$ and time during the first 3 min of recovery.

Results: Peak $\dot{V}o_2$ increased significantly in the exercise group (19.4 ± 3.0 mL/kg/min vs 25.1 ± 4.7 mL/kg/min, p < 0.05), whereas no change was observed in control subjects. The $\dot{V}o_2$ half-time in recovery was reduced slightly after the study period in both groups (108.7 ± 33.1 to 102.1 ± 50.5 s in the exercise group and 122.3 ± 68.7 to 107.5 ± 36.0 s in the control group); neither the change within or between groups was significant. The degree to which $\dot{V}o_2$ was prolonged in recovery was inversely related to measures of exercise capacity (peak $\dot{V}o_2$, watts achieved, and exercise time; r = − 0.48 to − 0.57; p < 0.01) and directly related to the peak ventilatory equivalents for oxygen (r = 0.59, p < 0.01) and carbon dioxide (r = 0.57, p < 0.01).

Conclusion: Two months of high-intensity training did not result in a faster recovery of $\dot{V}o_2$ in patients with reduced ventricular function. This suggests that adaptations to exercise training manifest themselves only during, but not in, recovery from exercise.   *(CHEST 2001; 120:1206–1211)*

Key words: chronic heart failure; exercise training; oxygen uptake

Abbreviations: ACE = angiotensin-converting enzyme; EPOC = excess postexercise oxygen uptake; $\dot{V}E$ = minute ventilation; $\dot{V}co_2$ = carbon dioxide production; $\dot{V}o_2$ = oxygen uptake

Exercise intolerance remains a hallmark of chronic heart failure. Treatment strategies, including angiotensin-converting enzyme (ACE) inhibition,[1,2] β-blockade,[3–5] and exercise training[6] have been demonstrated to improve symptoms and exercise capacity in patients with chronic heart failure. The addition of exercise training as a therapeutic option in patients with chronic heart failure represents a departure from past decades in which these patients were generally excluded from formal exercise training programs due to concerns about safety, and reservations about whether they could derive any benefits. A substantial body of evidence has been published[6,7] in the 1990s documenting the efficacy and safety of exercise training in these patients. Benefits of exercise training that have been documented[6–8] include improvements in peak oxygen uptake ($\dot{V}o_2$), 6-min walk time, autonomic balance, quality of life, and endothelial function.

Studies[9–14] have observed that time to recovery of $\dot{V}o_2$ after exercise (postexercise $\dot{V}o_2$ kinetics) is delayed in patients with chronic heart failure, and the degree to which this response delayed is related to the severity of chronic heart failure. The delay in postexercise $\dot{V}o_2$ kinetics in patients with chronic

heart failure appears to be related to a delay in the recovery of energy stores in the active muscle, as demonstrated[9] using nuclear magnetic resonance spectroscopy. A faster adjustment of $\dot{V}O_2$ to a given workload at the onset of exercise after training has been demonstrated in normal subjects,[15–18] as has an improvement in $\dot{V}O_2$ recovery time.[15] In patients with chronic heart failure, an improvement in this response might be reflected clinically in lessened dyspnea after exertion, as a marker for lessened disease severity, and presumably by an improvement in prognosis, since this index has been suggested[10] to predict outcomes in this condition.

To our knowledge, no controlled studies have been performed to assess the effects of an exercise training program on $\dot{V}O_2$ kinetics in recovery in patients with reduced ventricular function. We performed the present study to: (1) further characterize the behavior of $\dot{V}O_2$ recovery in these patients, and (2) investigate the effects of exercise training on recovery kinetics of $\dot{V}O_2$ in patients with reduced ventricular function who were referred to a residential cardiac rehabilitation facility in Switzerland.

MATERIALS AND METHODS

Patients

Twelve male patients (mean age, 56 ± 5 years) participated in the exercise group, and 12 male patients (mean age, 55 ± 7 years) participated in the control group after giving written informed consent. Clinical characteristics of the two groups are outlined in Table 1. All patients had sustained a recent myocardial infarction, and their hospital course included the diagnosis of heart failure. Nine of the 12 patients (75%) in the exercise group and 11 of the

Table 1—Patient Characteristics*

Characteristics	Exercise Group (n = 12)	Control Group (n = 12)
Age, yr	56.1 ± 5	55.7 ± 7.0
Height, cm	172.7 ± 6.0	167.9 ± 5.0
Weight, kg	76.9 ± 7.5	70.7 ± 10
Ejection fraction, %	31.5 ± 6.8	33.1 ± 6.0
Maximal $\dot{V}O_2$, mL/kg/min	19.4 ± 3.0	18.7 ± 4.1
Pulmonary function		
FEV_1	2.66 ± 0.45	2.63 ± 0.68
FEV_1, % of normal	80.4 ± 11.7	81.9 ± 23.2
FVC	3.68 ± 0.63	3.30 ± 0.83
FVC, % of normal	88.8 ± 10.6	83.1 ± 20.6
Peak expiratory flow, % of normal	80.8 ± 25.0	76.1 ± 31.0
Medications, No.		
Digoxin	8	7
ACE inhibitors	12	12
Diuretics	6	6
Others	5	6

*Data are presented as mean ± SD unless otherwise indicated.

12 patients (92%) in the control group underwent bypass surgery following their myocardial infarction. Prior to hospitalization, none of the patients had a previous history of heart failure. The presence of reduced ventricular function was documented by signs, symptoms, and angiographic evidence (ejection fraction < 40%) at the time of randomization. All patients had stable symptoms following their myocardial infarction, surgery, or both prior to randomization. All patients were receiving an ACE inhibitor, and none were receiving a β-blocker during the study period. The duration between the myocardial event and the initial test was 36.1 ± 14 days for patients randomized to the trained group and 35.0 ± 6 days for patients in the control group. At the time of the initial exercise test, all patients were in New York Heart Association class II or class III. All were limited by fatigue or dyspnea on baseline exercise testing, and none had clinical evidence of pulmonary disease.

Study Design

Group assignment was randomized. Patients in both groups underwent standard pulmonary function tests and cardiopulmonary exercise testing at baseline (approximately 1 month after myocardial infarction, bypass surgery, or both) and 2 months following randomization to exercise training or usual care.

Exercise Training

After stabilization and initial testing, patients in the exercise group resided in a rehabilitation center in Seewis, Switzerland, for a period of 8 weeks. Seewis is a small village in the mountains with an elevation of 3,500 feet. The center has its own staff of physicians, consisting of a medical director and three interns/residents. Program components included education, exercise, and low-fat meals prepared three times daily by the rehabilitation center cook. Two approximately 1-h outdoor walking sessions daily were performed, once in the morning and once in the afternoon. Walking intensity was stratified into four levels based on clinical status, exercise capacity, and performance on a 500-m walking test (50-m increase in altitude) on a nearby hill. The patients were accompanied by an exercise leader and a physician during these walking sessions. A van equipped with emergency supplies followed the group.

In addition to these walking periods, the 12 patients in the exercise group performed four 45-min periods of monitored stationary cycling per week. The cycling sessions were designed to elicit an intensity equal to roughly 60 to 70% of the patient's peak $\dot{V}O_2$, and were increased progressively over the 2 months as tolerated. Each of these sessions was monitored closely by a medical resident at the rehabilitation center. Heart rate, workload, and perceived exertion were recorded every 5 min; adjustments were made in exercise intensity as appropriate. Control patients received usual clinical follow-up at home, and did not undergo any formal exercise program.

Exercise Testing

Maximal exercise tests were performed at baseline and 2 months after randomization to the training or control groups. On the day of testing, patients were requested to abstain from food, coffee, and cigarettes for 3 h prior to the test. Standard pulmonary function tests were performed. Maximal exercise testing was performed on an electrically braked cycle ergometer using an individualized ramp protocol. Briefly, this test entails choosing an individualized ramp rate to yield a test duration of approximately 10 min.[19] Arterial blood lactate samples were drawn every minute throughout the test. A 12-lead ECG was monitored continuously,

and BP was measured manually every minute during exercise and throughout the recovery period. The patient's subjective level of exertion was quantified every minute using the Borg 6 to 20 scale.[20] All tests were continued to volitional fatigue/dyspnea. Respiratory gas exchange variables were acquired continuously throughout exercise using the Schiller CS-100 metabolic system (Schiller AG; Baar, Switzerland). Gas exchange variables analyzed included $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$), respiratory rate, tidal volume, oxygen pulse, and respiratory exchange ratio. The lactate threshold was chosen using a plot of the minute-by-minute lactate responses vs time by two experienced observers (J.M. and P.D.).

The constant decay of $\dot{V}O_2$, expressed as the slope of a single exponential relation between $\dot{V}O_2$ and time during the first 3 min of recovery, was calculated using with following equation:

$$y = y0 + Ae(-x/t)$$

where y is $\dot{V}O_2$, $y0$ is $\dot{V}O_2$ at time zero, (the beginning of the recovery phase), A and e are constants, x is the time elapsed, and t is the constant decay (Origin, version 2.5; Microcal Software; Northampton, MA). Breath-by-breath values that fell outside the 95% confidence limits of the calculated z distribution were excluded. The time constant indicates the time required to achieve 63.2% of the difference between peak and baseline values. The recovery half-time represents the time required for a 50% fall from the peak $\dot{V}O_2$ value.

Statistics

Statistical software (Statgraphics Plus, Version 4; Statistical Graphics Corporation; Bethesda, MD) was used to perform multivariate analysis of variance procedures comparing hemodynamic, gas exchange, and recovery responses between groups. *Post hoc* multiple comparison procedures were performed using the Scheffe method. Data are presented as mean ± SD.

RESULTS

No differences were observed between the two groups initially in clinical or demographic data, including age, height, weight, resting BP, pulmonary function, ejection fraction, or maximal $\dot{V}O_2$ (Table 1). Ejection fraction was unchanged in both the trained and control groups across the study period. No untoward events occurred during any of the exercise testing or training procedures during the 2 months of observation. Patients in the exercise group were closely monitored for heart rate, workload, and perceived exertion during their stationary cycling sessions and only generally during walking sessions. During monitored cycling over the 2-month training period, the mean percentage of maximal heart rate maintained was 83 ± 6%, the mean percentage of maximal workload was 78 ± 7%, and perceived exertion averaged 15.2 ± 2.

Maximal Exercise Testing

Exercise and ventilatory gas exchange data for each group are presented in Table 2. Both groups achieved mean maximal respiratory exchange ratios of approximately 1.20 and mean perceived exertion levels of approximately 19 on pretests and posttests, suggesting that maximal efforts were generally achieved. No differences were observed within or between groups in maximal heart rate or BP. The exercise group demonstrated a 29% increase in

Table 2—Exercise and Gas Exchange Data*

Variables	Exercise (n = 12)		Control (n = 12)		p Value Between Groups
	Before	After	Before	After	
Rest					
Heart rate, beats/min	83 ± 15	71 ± 15	87 ± 13	77 ± 14	0.87
Systolic BP, mm Hg	132 ± 18	137 ± 13	140 ± 16	133 ± 19	0.35
Diastolic BP, mm Hg	84 ± 11	83 ± 12	85 ± 9	78 ± 9	0.19
Maximal exercise					
Heart rate, beats/min	144 ± 22	150 ± 25	144 ± 15	141 ± 18	0.53
Systolic BP, mm Hg	170 ± 23	180 ± 23	177 ± 28	176 ± 22	0.47
Diastolic BP, mm Hg	86 ± 13	87 ± 18	90 ± 9	89 ± 16	0.76
$\dot{V}O_2$, mL/min	1,493 ± 260	1,872 ± 401	1,315 ± 281	1,332 ± 292	0.08
$\dot{V}O_2$, mL/kg/min	19.4 ± 3.0	25.1 ± 4.7†	18.7 ± 4.1	19.1 ± 4.5	0.06
$\dot{V}E$, L/min	64.5 ± 12.3	77.2 ± 10.7‡	50.1 ± 9.5	50.7 ± 12.1	0.11
$\dot{V}CO_2$, L/min	1.788 ± 0.322	2.274 ± 0.463†	1.602 ± 0.359	1.621 ± 0.436	0.06
$\dot{V}E/\dot{V}O_2$	43.6 ± 6.0	42.5 ± 7.0	39.6 ± 9.5	39.4 ± 10.6	0.97
$\dot{V}E/\dot{V}CO_2$	36.1 ± 2.6	34.8 ± 5.0	32.5 ± 7.3	32.3 ± 7.0	0.67
Respiratory exchange ratio	1.20 ± 0.13	1.22 ± 0.06	1.22 ± 0.11	1.19 ± 0.12	0.36
Lactate, mmol/L	4.41 ± 1.1	5.64 ± 1.1	4.69 ± 1.3	4.63 ± 2.0	0.12
Exercise time, min	9.4 ± 1.7	13.1 ± 2.2‡	9.2 ± 2.0	10.1 ± 2.1	0.01
Perceived exertion	18.7 ± 0.94	18.8 ± 0.87	18.8 ± 0.90	18.8 ± 0.80	0.81
W	129.9 ± 20.2	175.3 ± 31.0‡	113.7 ± 28.0	118.1 ± 30.2	0.02

*Data are presented as mean ± SD.
†p < 0.05 vs previous test within group.
‡p < 0.05 vs previous test within group.

maximal $\dot{V}O_2$ (19.4 ± 3.0 to 25.1 ± 4.7 mL/kg/min, p < 0.01). Concomitant increases in maximal $\dot{V}E$, $\dot{V}CO_2$, exercise time, and watts achieved were observed in the exercise group. No differences between tests were observed among control patients in maximal $\dot{V}O_2$, exercise time, or watts achieved.

$\dot{V}O_2$ at the lactate threshold increased significantly (by 35%, p < 0.01) after the training period in the exercise group. Conversely, small but insignificant decreases were observed in control subjects. Similar increases in exercise time and watts achieved at the lactate threshold were observed in patients in the exercise group, whereas the control group demonstrated small decreases in these variables. No differences were observed within or between groups in heart rate, systolic or diastolic BP, $\dot{V}E$, $\dot{V}CO_2$, respiratory exchange ratio, lactate, or perceived exertion at the lactate threshold.

$\dot{V}O_2$ time constants and half-time values in recovery for both groups are presented in Table 3, and the individual values for the half-time responses in recovery among trained subjects are illustrated in Figure 1. Both groups demonstrated decreases in these variables over the study period, but none of the differences were significant within or between groups. The time required for $\dot{V}O_2$ to recover from exercise was generally longer as fitness was reduced; significant inverse relationships were observed between $\dot{V}O_2$ half-time in recovery and maximal $\dot{V}O_2$ ($r = -0.57$, p < 0.01), exercise time ($r = -0.48$, p < 0.05), watts achieved ($r = -0.53$, p < 0.01), and maximal heart rate ($r = -0.42$, p < 0.05). Half-time in recovery was directly related to maximal $\dot{V}E/\dot{V}CO_2$ ($r = 0.57$, p < 0.01) and $\dot{V}E/\dot{V}O_2$ ($r = 0.59$, p < 0.01).

DISCUSSION

The capacity for patients with chronic heart failure to adapt to a training program are now recognized to be similar to post-myocardial infarction patients without reduced ventricular function.[6–8] Among the benefits of training in patients with reduced ventricular function are improvements in the ventilatory response to exercise,[21] but the effects of training on ventilation in recovery from exercise are unknown. The improvement in the ventilatory response to exercise after training has been attributed largely to a reduction in lactate accumulation, but improved matching of ventilation to perfusion in the lung and other factors may contribute.[21–23] The delayed time constants of $\dot{V}O_2$ and ventilation during recovery in patients with chronic heart failure have been explained by a delay in the recovery of energy stores in the muscle, as recently demonstrated using ^{31}P nuclear magnetic resonance spectroscopy,[9] although other factors, such as skeletal muscle metabolic abnormalities, microcirculatory changes, sustained hyperpnea, carbon dioxide retention, prolonged recovery of cardiac output, and increased cost of breathing[9–14] may contribute to the characteristic response observed during recovery from exercise in patients with chronic heart failure.

Because exercise training has been shown to partially normalize skeletal muscle metabolic characteristics in patients with chronic heart failure,[24,25] and also abnormal ventilatory responses to exercise,[21–23] it follows that a program of training would improve oxygen kinetics in recovery. The rate at which $\dot{V}O_2$ recovers from exercise has been used as an index of oxidative capacity in healthy subjects,[9,10,12,15,26] and a growing body of literature suggests that $\dot{V}O_2$ kinetics in recovery are a marker of skeletal muscle oxidative capacity in patients with chronic heart failure.[9–13] As reported by others,[10–12] we observed significant inverse relationships between the extent to which $\dot{V}O_2$ was prolonged in recovery and measures of exercise tolerance (peak $\dot{V}O_2$, watts achieved) and hyperventilation ($\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$). To our knowledge, the present study is the first to assess in a controlled fashion the effects of exercise training on recovery kinetics in patients with reduced ventricular function.

At baseline, the $\dot{V}O_2$ half-times in recovery (mean, 110 ± 7 s) we observed were similar to those previously reported in patients with moderate-to-severe chronic heart failure,[10–12] which are substantially higher than those reported in normal subjects[11,15,26] and those with coronary artery disease.[11,27] Why exercise training did not improve $\dot{V}O_2$ recovery time

Table 3—$\dot{V}O_2$ Time Constants and Half-Time Values in Recovery From Exercise in the Trained and Control Groups*

Variables	Exercise		Control		p Value Between Groups
	Before	After	Before	After	
Time constant	156.8 ± 47.8	147.3 ± 72.9	176.5 ± 99.1	155.2 ± 52.0	0.78
Half-time	108.7 ± 33.1	102.1 ± 50.5	122.3 ± 68.7	107.5 ± 36.0	0.78

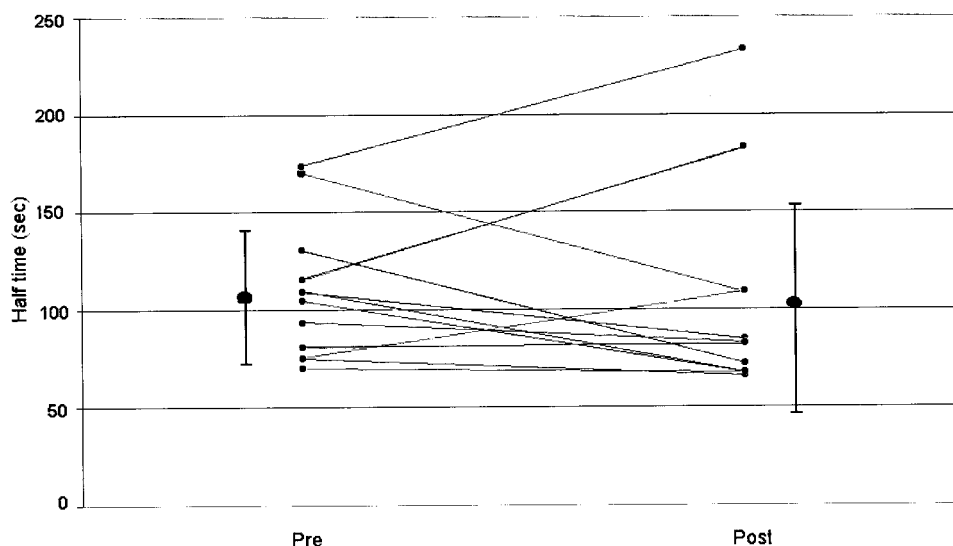*Data are presented as mean seconds ± SD.

FIGURE 1. Individual half-time recovery responses in subjects in the exercise group before (pre) and after (post) training. Error bars represent mean ± SD.

in the present study, despite the effects of training on peak $\dot{V}O_2$, is unclear. Previous studies have demonstrated that exercise training results in a faster recovery of $\dot{V}O_2$ from maximal or submaximal exercise in normal subjects,[15] patients with valvular heart disease,[28] and in patients with spinal cord injury subjected to functional electrical stimulation training.[29] However, such data in patients with chronic heart failure are lacking. We did not measure $\dot{V}O_2$ kinetics in response to submaximal exercise, as these patients were tested in a standard fashion as part of their participation in a cardiac rehabilitation program. It could be argued that the higher peak $\dot{V}O_2$ values after training altered the slope of the decline in $\dot{V}O_2$ during recovery, and masked any potential benefit reflected by the recovery-time constant. Interestingly, however, the time constant in recovery has generally been considered to be independent of the exercise level in studies using constant work rates.[9,13,30] Cohen-Solal et al[9] reported that the exercise level did not affect $\dot{V}O_2$ half-time in recovery when $\dot{V}O_2$ was > 50% of maximum. Similarly, Zanconato and coworkers[30] reported that the time constant in recovery from brief, high-intensity exercise was independent of the work rate, particularly when the work rate was above the ventilatory threshold.

We hypothesized that a reduction in the time constant of $\dot{V}O_2$ in recovery, implying a faster return of $\dot{V}O_2$ to the resting state, would have been an additional benefit of exercise training in patients with reduced ventricular function. Had such a response been observed, a reduction in what has been classically termed the *O₂ debt* or *excess postexercise $\dot{V}O_2$* (EPOC) could be added to a growing list of benefits

of exercise training in these patients.[6] Although the mechanism underlying the EPOC has been the subject of many different interpretations,[26] a reduction in the $\dot{V}O_2$ recovery time constant, and thus the EPOC, would certainly be related to a faster recovery from dyspnea after a bout of exercise, permitting a patient to perform more, or for a longer period of time, his or her daily activities. The fact that we did not observe a change in the $\dot{V}O_2$ recovery time constant after training may be due to characteristics unique to our population, or the method that patients were tested that negated such an effect. The use of a more complex modeling technique[31] or a longer recovery period may have reduced the variability and resulted in a better fit to the recovery data. We did observe a substantial degree of variability in the responses (Fig 1), and it could be argued that our sample size lacked adequate power. However, our training responses were considerable, and the control group exhibited a small reduction in the $\dot{V}O_2$ time constant, which was similar to that observed in the trained group.

Limitations

The population studied had reduced ventricular function after a myocardial infarction, but may not be representative of other studies in which the disease was more chronic or ventricular function was more severely reduced. As mentioned, the study population was small. Although we observed a significant training effect, a larger sample size may be needed to appropriately assess recovery $\dot{V}O_2$. Lastly, there is some debate as to whether a single exponen-

tial relation or multiexponential fitting for $\dot{V}O_2$ in recovery is most appropriate, although the majority of studies[9,10,12,27,28] assessing patients with reduced ventricular function have used the single exponential model, as we did.

Summary

Two months of high-intensity exercise training did not result in an improvement in $\dot{V}O_2$ kinetics in the recovery period from exercise in patients with reduced ventricular function following a myocardial infarction, despite a considerable improvement in peak $\dot{V}O_2$. This finding implies that ventilatory gas exchange adaptations to exercise training in patients with reduced ventricular function manifest themselves only during, but not in recovery from acute exercise.

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